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(54) Intraocular dosage compositions and method of use.

(57) A controlled release injectable intraocular dosage composition comprises an aqueous solution of
a pharmaceutical compound or non-toxic pharmaceutically acceptable salt thereof and
an ophthalmologically acceptable, non-toxic, viscosity-increasing polysaccharide.
The polysachharide is preferably a hyaluronic acid or a mixture of a hyaluronic acid and chondroitin sulfate.

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not be an antigen which will provoke an immune response by the organism, with consequent damage to the surrounding tissue. A preferred viscosity-increasing polysaccaride is hyaluronic acid, which is a naturally-occurring polymer of D-glucuronic acid and N-acetyl-D-glucosamine. Hyaluronic acid is found in animal tissues such as umbilical cord, vitreous humor, synovial fluid, rooster comb and the like, and also in certain bacteria, such as group A and C hemolytic streptococci. It is generally obtained on a commercial scale by extraction from umbilical cord or rooster combs. The molecular weight of the naturally occurring polymer ranges from about 50,000 to about 8,000,000, depending on the source and method of isolation. One type of hyaluronic acid which may be utilized is an ultrapure, non-inflammatory hyaluronic acid prepared as disclosed in Balasz, U.S. Patent 4,141,973. A particularly preferred hyaluronic acid is an ultrapure polymer having a molecular weight less than 750,000 which is dissolved in an isotonic aqueous solution substantially devoid of electrolytes. Such a solution has a sufficiently high viscosity to achieve the beneficial effects of the composition of this invention, and indeed has a viscosity comparable to that of a solution of a hyaluronic acid having a substantially higher molecular weight, but which is formulated with the conventional sodium chloride and phosphate buffer electrolytes.

The intraocular dosage composition of this invention should have a viscosity sufficient to prevent substantial diffusion of the drug contained therein from the site at which the composition is implanted. Evidently, the exact viscosity is not critical and the skilled practitioner can select the desired viscosity by incorporating more or less of the polysaccharide into the intraocular medication composition.

The pharmaceutical compound which is contained in the intraocular medication composition of the invention may be any drug which is used in treating a condition of the ocular tissues. For treating bacterial endophthalmitis the composition will contain an amount of an antibiotic effective to combat the bacterial infection. The amount will evidently vary according to the particular antibiotic used and the selection of the antibiotic and the amount thereof in the composition of the invention is within the routine capability of the skilled practitioner. Suitable antibiotics include penicillins, cephalosporins, aminoglycosides, e.g. gentamicin, tetracycline and the like. Antibiotics usable in the compositions and method of this invention may be found in the discussion of antibiotics found in Remington's Practice of Pharmacy, A. Osol, Ed., 16th Ed., Mack Publishing Co., Easton, Pennsylvania (1980), pages 1123-1146.

Another condition which is usefully treated by intraocular injection of the composition of this invention is intraocular inflammation, e. g., uveitis. For treatment of inflammatory conditions the composition of the invention will contain an antiinflammatory drug, e.g., a steroid or non-steroid antiinflammatory drug. The amount of drug used in the composition of the invention for treating inflammation will vary depending on the choice of drug and the extent and location of the inflammation within the eye. The selection of the antiinflammatory drug and the concentration to be used in the composition of the invention is within the routine competence of the skilled practitioner. Suitable antiinflammatory steroids may be found among those listed in Remington's Practice of Pharmacy, A. Osol, Ed., 16th Ed., Mack Publishing Co., Easton, Pennsylvania (1980), pages 901-912. Non-steroidal antiinflammatory drugs may be found in this work on pages 912-913. Typical steroidal antiinflammatory drugs include dexamethasone, beclomethasone, betamethasone and the like. Typical non-steroidal antiinflammatory drugs include indomethacin, ibuprofen, and the like

The invention will now be illustrated by the following example which compares the efficacy of intraocular medication by injection using a conventional isotonic saline vehicle and using the compositons of this invention. The example is only illustrative and is not intended to be interpreted as limiting the scope of the invention which is defined only by the appended claims.

Example

This example illustrates the antiinflammatory effect of dexamethasone when administered in the composition of this invention compared with its administration in a conventional saline solution.

An inflammatory condition of the eye was produced in the New Zealand White rabbit by the following procedure. Rabbits weighing 2.2 kg to 3.6 kg were used. They were sensitized to bovine serum albumin proteins by subcutaneous injections given three times a day at two day intervals. Three days after the last sensitizing dose one eye of each animal was challenged by an intravitreal injection of antigen. Prior to injection the eyes were anesthetized, the posterior portion of the globe was exposed and 0.05 ml of antigen solution was injected into the central part of the vitreous from an 0.1 ml Hamilton syringe via a 30 gauge nedle. Care was taken to avoid puncturing the exterior ocular musculature and visible blood vessels.

The result of the immunoreaction of the sensitized rabbits to the intravitreal challenge with antigen is an inflammation of the iris which can be observed and evaluated by conventional examination of the eye using a slit lamp. Twenty-four hours after challenge the eyes were examined by slit lamp and given a numerical score based on the observed congestion of the iris vessels, and the presence of iris edema. Before treatment was started the animals were sorted into groups by iris score, so that for each experiment the initial mean iris scores in the group for that experiment were similar. After the initial scoring and sorting of the animals into groups, the treatment was begun.

The inflammation was treated by administration of the steroid antiinflammatory drug dexamethasone. One group was treated by topical administration of dexamethasone in a commercially available suspension having a concentration of 0.1 %.

The inflammation was treated by intravitreal injection of physiological saline solution (control), dexamethasone sodium phosphate in saline, or dexamethasone sodium phosphate in an aqueous

IRIS INFLAMMATION: DOSE RESPONSE TO A SINGLE INTRAVITREAL DEXAMETHASONE INJECTION

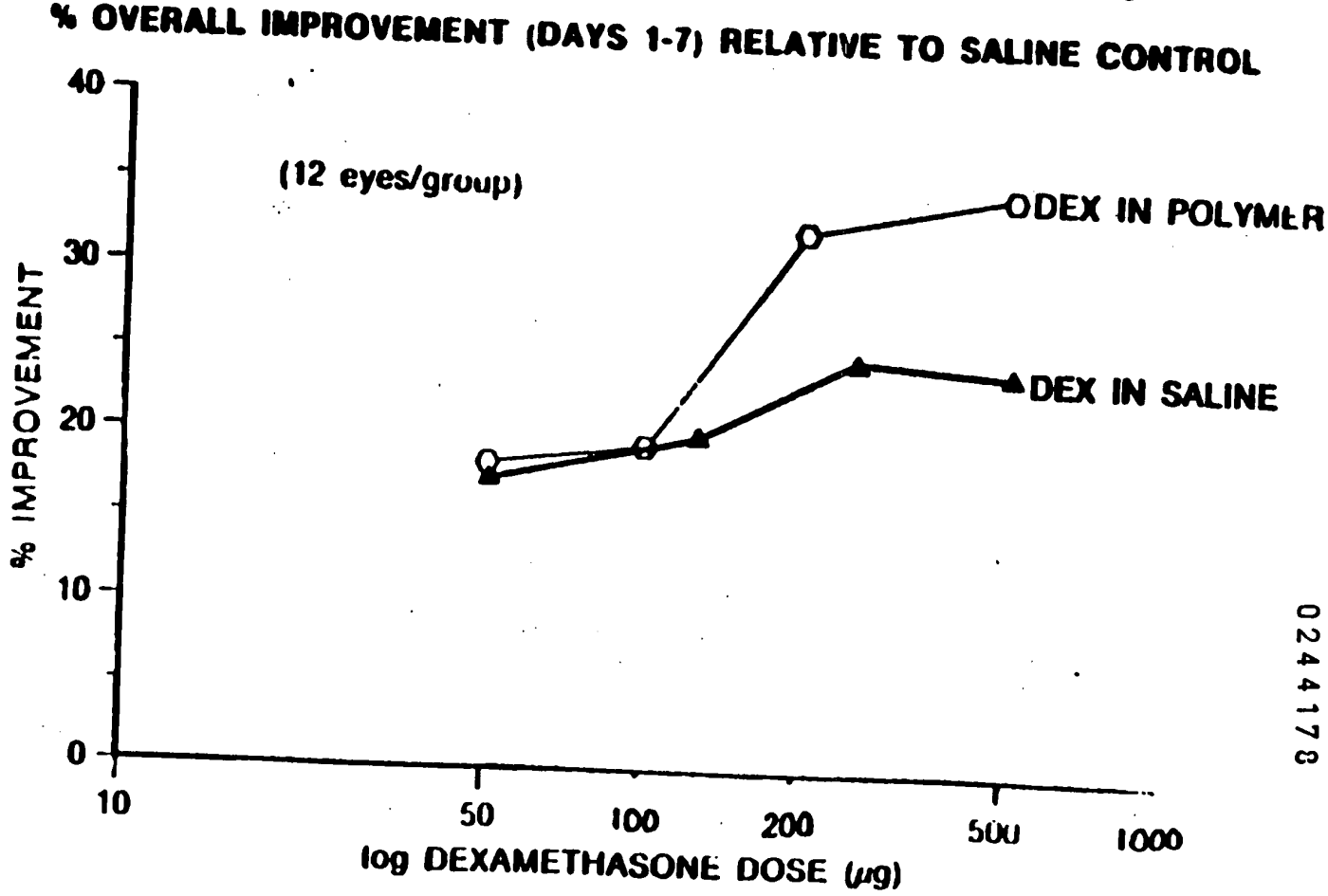

Figure 1

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Figure 2

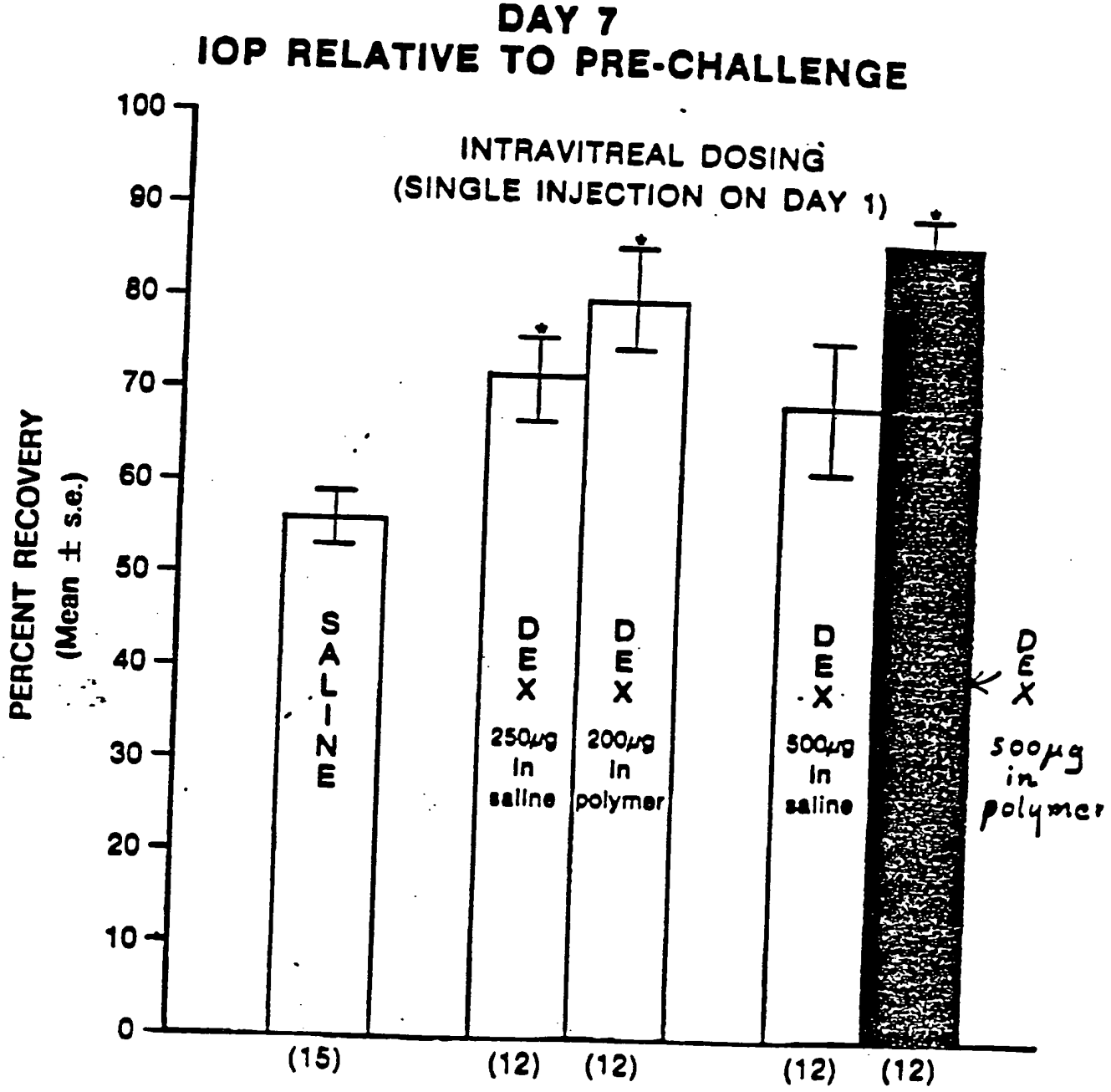

DAY 7
IOP RELATIVE TO PRE-CHALLENGE
INTRAVITREAL DOSING
(SINGLE INJECTION ON DAY 1)
PERCENT RECOVERY
(Mean ± s.e.)
100
90
80
70
60
50
40
30
20
10
0
SALINE
DEX 250µg in saline
DEX 200µg in polymer
DEX 500µg in saline
DEX 500µg in polymer
(15)
(12)
(12)
(12)
(12)

Figure 3

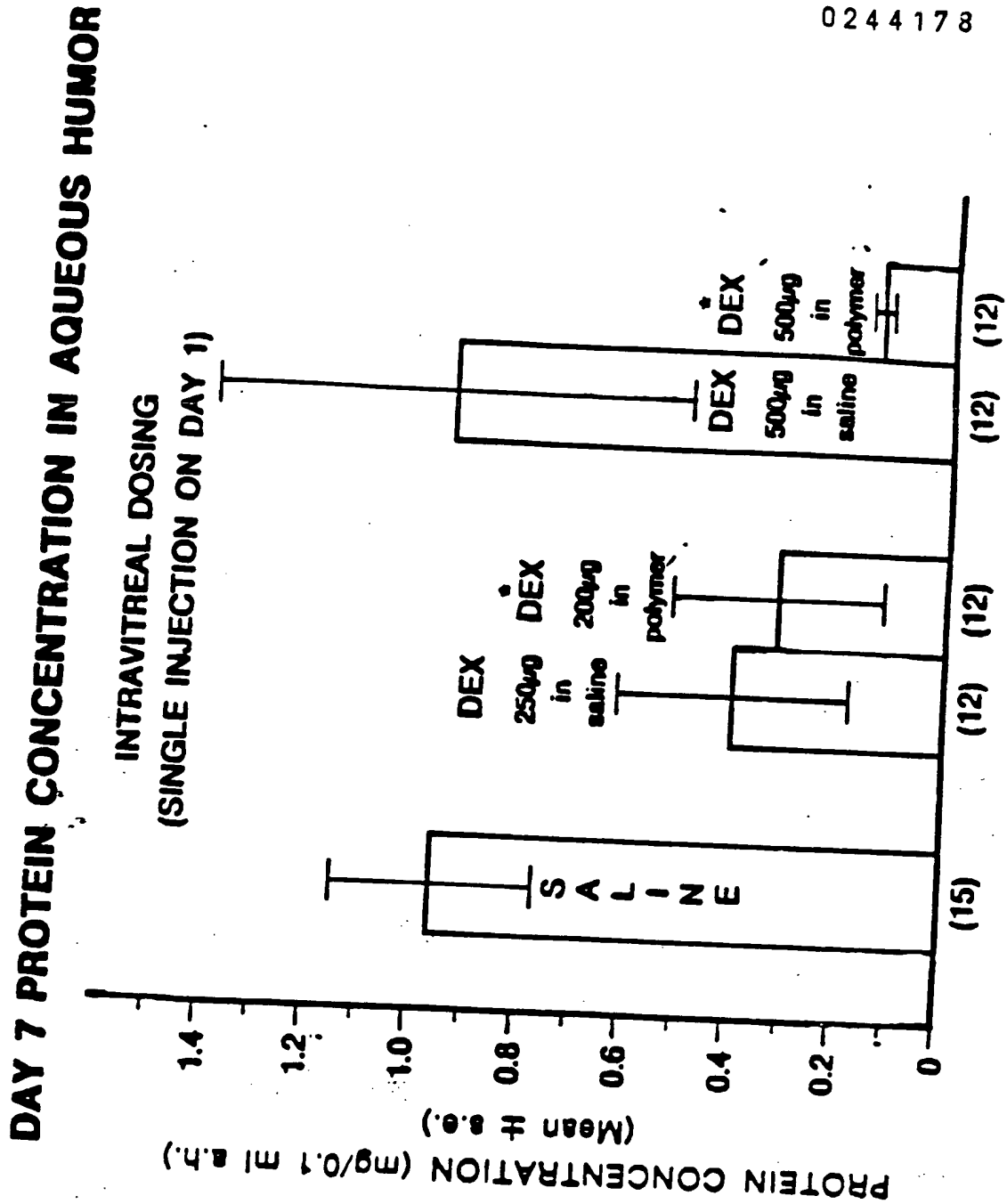
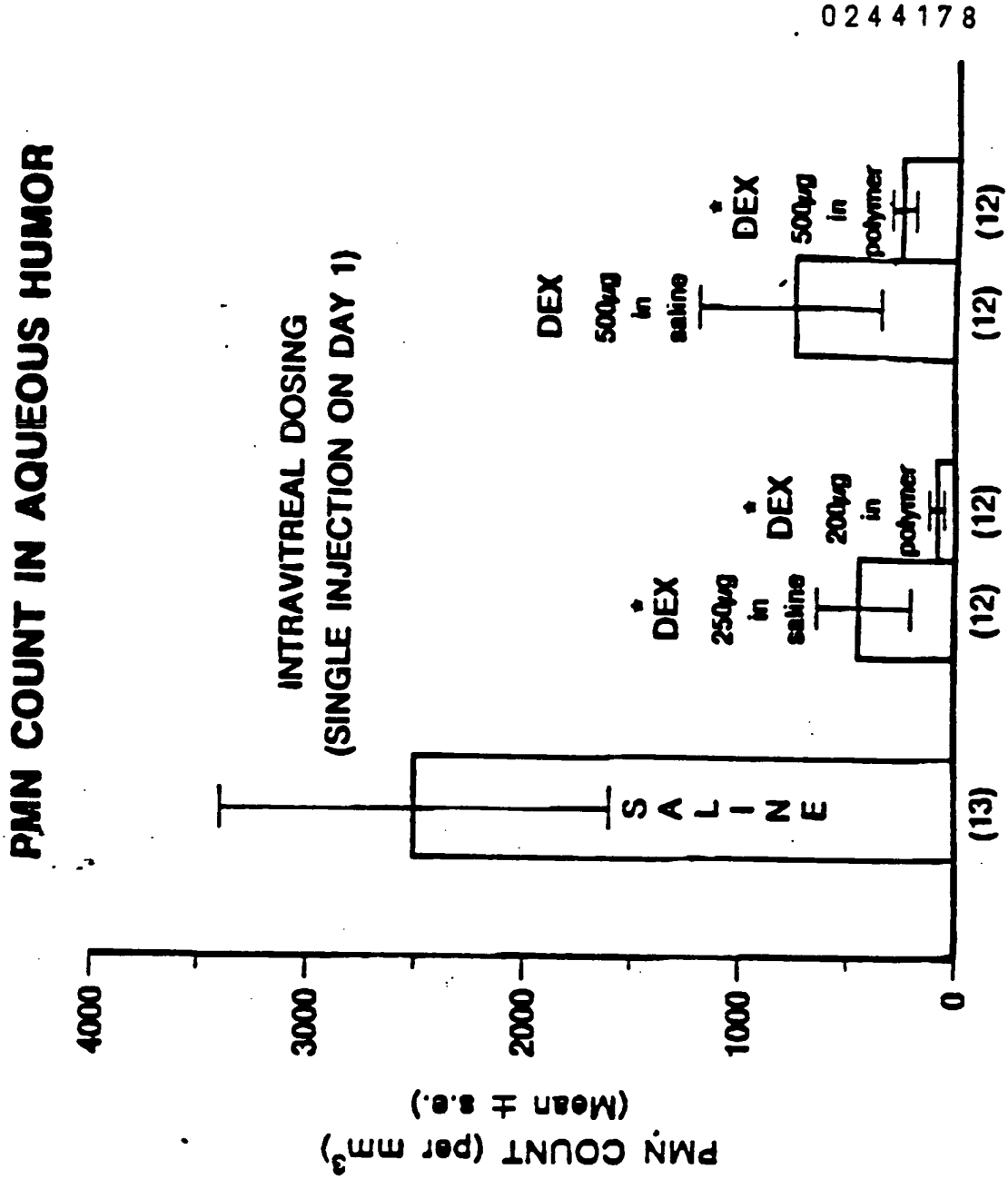

DAY 7 PROTEIN CONCENTRATION IN AQUEOUS HUMOR
INTRAVITREAL DOSING
(SINGLE INJECTION ON DAY 1)
PROTEIN CONCENTRATION (mg/0.1 ml a.h.)
(Mean ± s.e.)
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
SALINE
DEX 250µg in saline
DEX 200µg in polymer
DEX 500µg in saline
DEX 500µg in polymer
(15)
(12)
(12)
(12)
(12)

Figure 4


DAY 7
PMN COUNT IN AQUEOUS HUMOR
INTRAVITREAL DOSING
(SINGLE INJECTION ON DAY 1)
PMN COUNT (per mm³)
(Mean ± s.e.)
4000
3000
2000
1000
0
SALINE
(13)
DEX 250µg in saline
(12)
DEX 200µg in polymer
(12)
DEX 500µg in saline
(12)
DEX 500µg in polymer
(12)

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EUROPEAN SEARCH REPORT

Application Number

EP 87 30 3676

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 138 572 (FIDIA SpA) * Page 38, lines 1-18; examples 10-12; claims 1-14 * ---	1-3,5-9	A 61 K 9/08 A 61 K 47/00
E	EP-A-0 224 987 (BIOMATRIX, INC.) * Claims 1-24 * -----	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	07-11-1988	TZSCHOPPE, D.A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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